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| 10/537,188 | 06/02/2005 | Niall Gormley | 2713-1-015PCT/US | 1232 |

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| EXAMINER | |
|---|---|
| SHAW, AMANDA MARIE | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/537,188 | GORMLEY ET AL. | |
| | Examiner | Art Unit | |
| | Amanda Shaw | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11/18/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *4 and 27-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 27-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 18, 2009 has been entered.

Claims 4 and 27-36 are currently pending.

Claims 4, 35, and 36 have been amended.

### *Withdrawn Rejections*

2. The rejections made under 35 USC 103 in sections 5-7 of the Office Action of July 16, 2009 are withdrawn in view of amendments made to the claims and the applicant's arguments.

### *Claim Rejections - 35 USC § 103*

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejections are newly presented:

4. Claims 4, 27-31, and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balasubramanisn (WO 01/57248 Pub 9/2001) as evidenced by Cheeseman (US Patent 5302509 Issued 1994) and in view of Lackey (US Patent 5652126 Issued 1997) and Hong (US Patent 5747298 Issued 1998) .

Regarding Claims 4, 35, and 36 Balasubramanisn teaches a method comprising forming an array of polynucleotide molecules immobilized on a solid surface. Each polynucleotide has a hairpin loop structure wherein one end of hairpin loop structure acts as a primer and the other end of the hairpin loop structure acts as a template (page 3, lines 11-14 and page 4 line 28 to page 5 line 7). Balasubramanisn further teaches that the polynucleotides are attached to the array at a density of between $10^6$-$10^9$ sequences per $cm^2$ (page 4, line 9). Balasubramanisn also teaches determining the sequence of the template nucleic acids by synthesizing a complementary nucleic acid

strand. Specifically Balasubramanisn cites the method of Cheeseman as a suitable sequencing method (page 7, lines 24-31). The method of Cheeseman comprises contacting the template with fluorescently labeled 3' blocked nucleotide triphosphates, with each of the bases having a different fluorescent label and a polymerase. The DNA polymerase causes selective addition of only the complementary labeled NTP, thus identifying the next unpaired base in the unknown strand. The 3' blocking group is then removed, setting the system up for the next NTP addition and so on (Abstract). Thus Balasubramanisn as evidenced by Cheeseman teaches determining the sequence of the template nucleic acids by synthesizing a first complementary copy of each of the template sequences wherein said synthesizing involves repeated cycles of incorporating a single nucleotide into the first complementary copy and detecting incorporation of the single nucleotide into the first complementary copy on the array thereby performing a first round of sequencing to generate a sequence of the first complementary copy.

Regarding Claims 27 and 28 Balasubramanisn teaches a method wherein the template polynucleotides are attached to a double stranded anchor wherein the double stranded anchor is a self complementary hairpin (page 4 line 28 to page 5 line 7).

Regarding Claim 30 Balasubramanisn teaches that the $10^6$-$10^9$ different templates are individually resolvable (page 4, line 11).

Regarding Claim 31 Balasubramanisn teaches a method wherein the sequencing determination is carried out using cycles of incorporation and detection of fluorescently

labeled nucleotides. Specifically Balasubramanisn refers to the method of Cheeseman which teaches this (see Cheeseman abstract).

Regarding Claim 33 Balasubramanisn teaches a method which employs a polymerase enzyme to synthesize a complementary strand one base at a time. Specifically Balasubramanisn cites the method of Cheeseman which teaches using Taq polymerase (see Cheeseman Col 3, line 67).

Further regarding claim 35 it is noted that the recitation of "a method for simultaneously sequencing a complete genome" merely sets forth the intended purpose of the claimed method, but does not limit the scope of the claims. As noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, the process steps are able to stand alone and the preamble limitation is not accorded patentable weight.

Balasubramanisn does not teach a method further comprising removing the complementary copy of each of the template sequences from the array thereby regenerating the immobilized single stranded template molecules on the array (clms 4,

35, and 36 (step c)). Further Balasubramanisn does not teach performing a second round of sequencing of each of the immobilized single stranded template nucleic acid molecules regenerated in step (c) by synthesizing a second complementary copy of each of the template sequences, wherein said synthesizing involves repeated cycles of incorporating a single nucleotide into the second complementary copy and detecting incorporation of the single nucleotide into the second complementary copy on the array, thereby generating a sequence of the second complementary copy (clms 4, 35, and 36 (step d)). Balasubramanisn does not teach comparing the sequence of the first complementary copy detected in step (b) to the sequence of the second complementary copy detected in step (d) for each of the immobilized single stranded template nucleic acid molecules to confirm sequencing data of each of the immobilized single stranded template nucleic acid molecules (clms 4, 35, and 36 (step e)). Balasubramanisn does not teach a method wherein the double stranded anchor comprises a recognition site for a restriction endonuclease (clm 29). Further Balasubramanisn does not teach a method wherein the comparing step reduces random sequencing errors of the template sequences arising from the first round of sequencing (clm 34).

However Lackey teaches a method that comprises synthesizing a complementary copy of a nucleic acid sequence using a primer and a template sequence. Lackey further teaches that in instances where a DNA primer/template with a single 3' ribonucleotide is used, cleavage at the ribonucleotide residue, followed by separation and purification of the oligonucleotide product, results in a fully regenerated and reusable primer/template (Col 13, lines 26-31). Lackey further teaches that

cleavage may be performed using a site specific restriction endonuclease, alkaline hydrolysis or an endonuclease such as RNase (col 12, lines 42-47). Thus Lackey teaches a method comprising removing the complementary copy of a template sequence thereby regenerating the template and a method wherein the primer has a recognition site for a restriction endonuclease.

Additionally Hong teaches that researchers in the field of DNA sequencing often have to use several approaches to confirm their findings in order to avoid being misled by potentially erroneous sequence data. Hong teaches that sometimes researchers rely on repeating the same sequencing experiment with different DNA polymerases, or performing another sequencing reaction with the template that is complementary to the first single stranded DNA template, and comparing the results for possible discrepancies (Col 2, lines 47-55). Thus Hong teaches performing a second round of sequencing on the same template used in the first round of sequencing and comparing the sequence of the first complementary copy to the sequence of the second complementary copy in order to confirm sequence data. Since possible discrepancies were noted the method of Hong is being interpreted as a method that reduces random sequencing errors.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Balasubramanisn by removing the first complementary strand to regenerate the template molecule (as suggested by Lackey), resequencing the regenerated template molecule (as suggested by Hong), and comparing the sequence of the first complementary copy and the second

complementary copy to confirm sequence data (as suggested by Hong). Hong teaches that researchers in the field of DNA sequencing often have to use several approaches to confirm their findings in order to avoid being misled by potentially erroneous sequence data. Based on this teaching one of skill in the art performing the method of Balasubramanisn would have been motivated to remove the first complementary strand to regenerate the template molecule, resequence the regenerate template molecule, and compare the two sequences in order confirm their findings and avoid being misled by potentially erroneous sequence data. One of skill in the art would have had a reasonable expectation of success in doing so. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore the invention as a whole was prima facie obvious to one or ordinary skill in the art at the time the invention was made, as evidenced by the references.

5. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Balasubramanisn (WO 01/57248 Pub 9/2001) as evidenced by Cheeseman (US Patent 5302509 Issued 1994) and in view of Lackey (US Patent 5652126 Issued 1997) and Hong (US Patent 5747298 Issued 1998) as applied to claims 4 and 31 above and in further view of Barnes (WO 01/57249 Pub 8/2001).

The teachings of Balasubramanisn (evidenced by Cheeseman), Lackey, and Hong are presented above.

The combined references do not teach a method wherein the fluorescently labeled nucleotides are detected using a microscope with total internal reflection based imaging.

However Barnes teaches that using total internal reflection fluorescent microscopy it is possible to achieve wide field imaging with single polymer sensitivity. This allows arrays of greater than $10^7$ resolvable polymers per $cm^2$ to be used (page 6, lines 9-14).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Balasubramanisn (as evidenced by Cheeseman), Lackey, and Hong by using a microscope with total internal reflection to detect the incorporation of each fluorescently labeled nucleotide as suggested by Barnes. Barnes teaches it is possible to achieve wide field imaging with single polymer sensitivity and that this allows arrays of greater than $10^7$ resolvable polymers per $cm^2$ to be used. Therefore one of skill in the art would have been motivated to use the detection method disclosed by Barnes for the benefit of being able to detect a large number of individual fluorescent nucleotides present on the array.

## Response To Arguments

6. In the response filed November 18, 2009, the Applicants traversed the rejections based on the combination of Balasubramanisn (WO 01/57248 Pub 9/2001), as evidenced Cheeseman (US Patent 5302509 Issued 1994), Soper (US Patent 5846727) and Parker (US Patent 5565323). Since the rejections based on this particular

combination have been withdrawn the applicants arguments based on this particular combination will not all be addressed. Any argument which still pertains to the newly presented rejections will be addressed herein.

The Applicants state that the claims require "removing the complementary copy of each of the template sequences from the array, thereby regenerating the immobilized single stranded template molecules on the array" as recited in step (c) of claims 4 and 35 or "removing the complementary copy of each of the template sequences to recover an array of sequenced immobilized single stranded template nucleic acid molecules" as recited in step (c) of claim 36. The applicants argue that none of the references taken alone or in combination fail to teach or suggest regenerating immobilized single stranded template molecules on array.

In response to this argument it is noted that Balasubramanisn as evidenced by Cheeseman teaches determining the sequence of the template nucleic acids by synthesizing a first complementary copy of each of the template sequences wherein said synthesizing involves repeated cycles of incorporating a single nucleotide into the first complementary copy and detecting incorporation of the single nucleotide into the first complementary copy on the array thereby performing a first round of sequencing to generate a sequence of the first complementary copy. Balasubramanisn further teaches that the template nucleic acids are present on an array. While Balasubramanisn does not teach removing the complementary copy of each of the template sequences from the array, thereby regenerating the immobilized single stranded template molecules on the array, Lackey teaches a method comprising

extending a primer to produce a complementary copy of a template and removing the complementary copy of a template sequence. Specifically Lackey teaches that in instances where a DNA primer/template with a single 3' ribonucleotide is used, cleavage at the ribonucleotide residue, followed by separation and purification of the oligonucleotide product, results in a fully regenerated and reusable primer/template (Col 13, lines 26-31). Thus the combination of Balasubramanisn and Lackey suggests regenerating immobilized single stranded template molecules on an array which in turn makes it possible to perform a second round of sequencing each of the immobilized single stranded template molecules. Since the molecules are on an array it makes it possible to ascribe a complementary copy sequence read to a particular template molecule on the array.

Regarding the Lackey reference the applicants argue that Lackey has nothing to do with sequencing. They state that Lackey is directed to cleaving phosphorothioate oligonucleotides to generate relatively cleavage resistant phosphorothioate oligonucleotides having properties that facilitate their separation and purification after synthesis. Applicant's assert that this reference has nothing to do with sequencing because the sequence of the template is already known.

These arguments have been fully considered but are not persuasive. While Lackey may not be directed to "sequencing" per se, Lackey is not being relied upon to teach "sequencing" because it is taught by Balasubramanisn. The method of Lackey is relevant to the instant claims because the method of Lackey comprises synthesizing a complementary nucleic acid sequence using a template sequence and a primer that has

a recognition site for a restriction enzyme and then cleaving the primer at the recognition site, thereby producing a fully regenerated and reusable primer/template. The present claims also require synthesizing a complementary copy of a template and removing the complementary copy of a template thereby regenerating the original template. It is further noted that the rejection is based on Hong who teaches that researchers in the field of DNA sequencing often have to use several approaches to confirm their findings in order to avoid being misled by potentially erroneous sequence data. Hong teaches that sometimes researchers rely on repeating the same sequencing experiment with different DNA polymerases, or performing another sequencing reaction with the template that is complementary to the first single stranded DNA template, and comparing the results for possible discrepancies (Col 2, lines 47-55). Thus practioners in the art wishing to repeat the same sequence experiment with a different DNA polymerase or wishing to perform another sequencing reaction with the same DNA template would look for ways known in the art to regenerate a template molecule. Even though Lackey isn't directed to sequencing one would look to Lackey because Lackey teaches how to regenerate template molecules.

Regarding the claims rejected using Barnes as an additional reference the Applicants argue that Barnes does not cure the deficiencies of the other references.

This argument has been fully considered but is not persuasive. The newly presented rejections teach each and every claim limitation present in claims 4, 27-31 and 33-36. Further motivation to combine the references is present and has been provided. Barnes is only being cited for using a microscope with total internal reflection

to detect the incorporation of each fluorescently labeled nucleotide. Barnes teaches it is possible to achieve wide field imaging with single polymer sensitivity and that this allows arrays of greater than $10^7$ resolvable polymers per $cm^2$ to be used. Therefore it would have been obvious to use the detection method disclosed by Barnes for the benefit of being able to detect a large number of individual fluorescent nucleotides present on the array.

***Conclusion***

7. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634